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L3: Entry 111 of 148 File: USPT Oct 29, 2002

DOCUMENT-IDENTIFIER: US 6472421 B1
TITLE: Methods for treating, preventing, and reducing the risk of the onset of alzheimer's disease using an HMG CoA reductase inhibitor

Abstract Text (1):
Described are methods for treating, preventing, or reducing the risk of the onset of Alzheimer's disease by administering a therapeutically effective amount of an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase ("HMG CoA reductase inhibitor") to a patient who is at risk for a coronary or cerebrovascular event or at risk for Alzheimer's disease.

Brief Summary Text (7):
HMG CoA reductase is the enzyme catalyzing the early rate-limiting step in cholesterol biosynthesis, i.e., conversion of HMG-CoA to mevalonate. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. These complexes can be separated by density ultracentrifugation into high (HDL), intermediate (IDL), low (LDL), and very low (VLDL) density lipoprotein fractions. Triglycerides (TG) and cholesterol synthesized in the liver are incorporated into VLDLs and released into the plasma for delivery to pheripheral tissues. In a series of subsequent steps, VLDLs are transformed into IDLs and cholesterol-rich LDLs. HDLs, containing apolipoprotein A, are hypothesized to participate in the reverse transport of cholesterol from tissues back to the liver.

Brief Summary Text (8):
Clinical and pathological studies have shown that elevated levels of total cholesterol, low LDL-cholesterol (LDL-C), and apolipoprotein B (a membrane transport protein for LDL) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total cholesterol and LDL-C, and inversely with the level of HDL-C. Thus, HDLs have been characterized as "good" lipoproteins, while cholesterol-rich LDLs have been characterized as being less favorable.

Brief Summary Text (27):
A first target patient population for this invention is those patients having one or more risk factors for cardiovascular and/or cerebrovascular disease. The term "risk factor for cardiovascular or cerebrovascular disease" is defined as risk factors such as hypercholesterolemia, hypertension, diabetes, cigarette smoking, familial or previous history of coronary artery disease, cerebrovascular disease, cardiovascular disease, and being male. Hypercholesterolemia in this context means the patient's serum total cholesterol concentration is at least 5.2 mmol/liter (at least 200 mg/dl), and more preferably the patient's serum total cholesterol concentration is from about 200 to about 300 mg/dl. The term "cerebrovascular disease" includes such diseases as atherosclerosis of the intracranial and/or extracranial arteries, stroke, syncope, and transient ischemic attacks. The term "cardiovascular disease" includes such diseases as atherosclerosis of the coronary arteries, angina pectoris, myocardial infarction, sudden cardiac death, and heart failure.

Brief Summary Text (28):
A second target patient population for this invention is those patients at risk for AD. The term "at risk for AD" is defined as patients being over the age of 60 or patients having a predisposition for AD. AD predisposing factors identified or proposed in the scientific literature include (but are not limited to): (1) a genotype predisposing a patient to AD; (2) environmental factors predisposing a patient to AD; (3) past history of infection by viral and bacterial agents predisposing a patient to AD; and (4) vascular factors predisposing a patient to AD.

Brief Summary Text (30):
A third target population for this invention is any patient, regardless of whether the patient has a risk factor for cardiovascular and/or cerebrovascular disease, or whether the patient is at risk for AD. The goal of treating such a target population is to reduce that patient's risk for developing AD in the future.

Brief Summary Text (31):
A fourth target population for this invention is any mammalian species, such as dogs, cats, horses, cattle, etc.

Brief Summary Text (33):
The term, "HMG CoA reductase inhibitor," refers to any compound which inhibits the bioconversion of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonic acid catalyzed by the enzyme HMG CoA reductase. The inhibiting effect of any such compounds can be readily determined by those skilled in the art according to standard assays. This invention describes and references a number of HMG CoA reductase inhibitors. However, other HMG CoA reductase inhibitors will be known to those skilled in the art.

Brief Summary Text (48):
Appropriate controls can be designed in a manner known to one of ordinary skill in the art. Example 3 below sets out two exemplary types of controls for such studies. The prevalence of AD for each of the populations can be calculated and analyzed statistically using methods known to one of ordinary skill in the art. A marked reduction in the prevalence of AD in a population taking the HMG CoA reductase inhibitor being screened as compared to a control or as compared to other HMG CoA reductase inhibitors known to have no effect on the prevalence of AD identifies the inhibitor as useful in the methods of the invention.

Brief Summary Text (50):
Many references teach methods of in vitro screening of potential therapeutics for AD. For example, U.S. Pat. No. 5,721,106, for "In Vitro method for screening beta-amyloid deposition," teaches methods for screening agents that enhance or inhibit beta-amyloid aggregation or deposition onto tissue; U.S. Pat. No. 5,547,841, for "In vitro method for screening for drugs that inhibit production or degradation of human A4-amyloid," describes an in vitro method of screening for drugs that are potentially useful for treatment of Alzheimer's Disease; U.S. Pat. No. 5,441,870, for "Methods for monitoring cellular processing of beta-amyloid precursor protein in vitro," describes how to monitor the secretion of beta-amyloid from cultured cells to identify inhibitors of beta-amyloid production; U.S. Pat. No. 5,538,845, for "Beta-amyloid peptide production inhibitors and methods for their identification," describes how to identify likely candidates for use as drugs for treating beta-amyloid diseases, such as Alzheimer's disease; and U.S. Pat. No. 5,605,811, for "Methods and compositions for monitoring cellular processing of beta-amyloid precursor protein," notes that the cultured cells described therein can be used in testing for compounds that cause a change in the secreted amount of the soluble fragment of beta APP.

Brief Summary Text (55):
A preferred oral dosage form, such as tablets or capsules, contains the one or more

HMG CoA reductase inhibitors in an amount preferably from about 0.5 to about 100 mg, more preferably from about 5 to about 80 mg, and most preferably from about 10 to about 40 mg. The remainder of the tablet or capsule can contain a physiologically acceptable carrier or other materials according to accepted pharmaceutical practice. Preferred dosages of various HMG CoA reductase inhibitors are known in the art and are described in, for example, U.S. Pat. No. 5,807,834. Tablets can be scored to provide for fractional doses. Liquid formulations can also be prepared by dissolving or suspending active substances in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage.

Brief Summary Text (56):
The formulations described herein above are administered for as long as the patient (1) has a risk factor for cardiovascular and/or cerebrovascular disease, or (2) is at risk for AD, or (3) continues to manifest the symptoms, signs, or biomarkers of AD. Sustained release forms of such formulations, which can provide such amounts biweekly, weekly, monthly, and the like, may also be employed. A dosing period of at least one to two weeks is required to achieve minimal benefit and to monitor the effect of the medication on the patient.

Brief Summary Text (61):
A capsule may contain, in addition to the types of material listed above, a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For example, tablets or capsules may be coated with shellac, sugar, or both. A syrup of elixir may contain the active compound, water, alcohol or the like as the carrier, glycerol as solubilizer, sucrose as sweetening agent, methyl and propyl parabens as preservatives, a dye, and a flavoring such as cherry or orange.

Detailed Description Text (11):
A large study employing health care databases at three different hospitals in the United States examined the relationship between the frequency of AD and eight different medications, including the HMG CoA reductase inhibitors lovastatin (Mevacor.RTM.), pravastatin (Pravachol.RTM.), and simvastatin (Zocor.RTM.) ("Decreased Risk of Alzheimer's Disease Associated with HMG CoA Reductase Inhibitors," B. Wolozin et al., in press).

Detailed Description Text (18):
Alzheimer's disease was identified under the ICD-9-CM code of 331.0, but because other codes also apply to AD, the codes 331.2, 290.0, 290.10-13, 290.20 and 290.3 were also included as AD cases based on interviews with the physicians at each center who diagnosed or oversaw the diagnosis of patients with AD and on their coding practices for AD. The diagnosis of AD was made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) Work Group (McKhann et al., "Clinical Diagnosis of Alzheimer's Disease: Report of the NINCDS-ADRDA Work Group under the Auspices of Department of Health and Human Services Task Force on Alzheimer's Disease," Neurology, 34:939-944 (1984).) Each AD patient had received either a CT scan or MRI to exclude other diagnoses, and had been screened for other metabolic, toxic, or affective disorders that may produce dementia. In addition, all AD patients at the Phoenix and Loyola centers had a mini-mental score of 24 or lower (Folstein et al., "Mini-Mental State," A Practical Method For Grading The Cognitive State of Patients For The Clinican, J. Psychiat. Res., 12:189-198 (1975)), and at the Hines center all patients for whom a mini-mental test was available similarly had scores of 24 or less.

Detailed Description Text (31):
The study clearly showed that patients taking one or more HMG CoA reductase inhibitors had a dramatically lower risk of AD, thus indicating prevention of AD and treatment of existing AD, than the total population. Normally, a higher rate of

AD would be expected for this population because of the presence of one risk factor for AD (elevated cholesterol) and the increased likelihood of a second risk factor (heart disease). For the patients taking beta-blockers, and hence having the risk factor of heart disease, the risk of AD was higher than the total population. The degree of reduction found in this patient population (69.6%) compares favorably with other putative AD therapeutics: estrogen (25-31%); NSAIDs (0% to 60%); and alpha-tocopherol (52%).

Detailed Description Paragraph Table (1):
TABLE I Comparison of rates of AD with Administration of Various Medications Prevalence Prevalence Prevalence Prevalence Significance vs. # of Mean Of AD/1000 Of AD/1000 Of AD/1000 Of AD/1000 Std Lovastatin + Confidence Medication Patients Age Combined Hines Loyola Phoenix Error Pravastatin Intervals Lovastatin 4180 71 .+-. 1 3.6 2.5 6.4 8.2 0.002 Pravastatin 2326 72 .+-. 1 4.3 1.1 0 8.3 0.002 Lovastatin + 6506 72 .+-. 1 3.8 2.2 4.7 8.2 0.002 Pravastatin Simvastatin 3580 71 .+-. 3 11.2 N/A 8.1 11.2 0.002 <0.005 -11 to -4 Captopril 4616 73 .+-. 2 10.6 8.4 13.6 10.6 0.002 <0.0005 -10 to -4 Furosemide 15106 74 .+-. 1 8.9 9.0 16.7 14.1 0.001 <0.0005 -8 to -3 Atenolol 5340 72 .+-. 2 14.8 7.1 19.2 19.0 0.002 <0.0005 -14 to -8 Metoprolol 3799 72 .+-. 2 12.1 4.4 15.3 12.4 0.002 <0.0005 -12 to -5 Propanolol 1256 72 .+-. 2 17.5 3.9 42.4 20.7 0.002 <0.0005 -18 to -9 Beta comb. 10395 72 .+-. 2 14.1 5.9 22.8 16.6 0.002 <0.0005 -13 to -7 Total # of 56790 74 .+-. 1 12.8 8.1 11.7 29.0 0.001 <0.0005 -8 to -3 Patients Data from the three sites were combined to obtain an overall prevalence. Combined Prevalence refers to the total number of patients carrying the diagnosis of AD in comparison to the total number of patients on that particular medication. No patients on simvastatin were recorded at Hines. The Total # of Patients refers to the total number of patients in the databases less the number of patients on lovastatin or pravastatin. Mean Ages is the mean of the mean ages from # each site. The significance (P vs. P/L) was determined by chi square analysis with respect to the combined pool of Lovastatin and Pravastatin (Lovastatin + Pravastatin).

Other Reference Publication (1):
Graul A., et al., "Atorvastatin Calcium", Drugs of the Future, vol. 22(9), pp. 956-968 (1997).

Other Reference Publication (2):
Yankner Bruce A., "Mechanisms of Neuronal Degeneration in Alzheimer's Disease", Neuron, vol. 16, pp. 921-932, (May 1996).

CLAIMS:

1. A method for treating, preventing, or reducing the risk of Alzheimer's disease (AD) in a patient who has one or more risk factors for AD, comprising administering to a patient in need thereof a therapeutically effective amount of one or more inhibitors of the enzyme 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase, wherein: (a) the HMG CoA reductase inhibitor is not simvastatin (b) treatment results in a reduction or inhibition of onset of Alzheimer's disease, (c) the one or more risk factors are selected from the group consisting of hypercholesterolemia, coronary artery disease, family or previous history of coronary artery disease, hypertension, diabetes, cigarette smoking, cerebrovascular disease, cardiovascular disease, elevated serum cholesterol, heart disease, and male gender, and (d) the patient to be treated does not possess the APOE 4 gene.

5. A method for treating, preventing, or reducing the risk of Alzheimer's disease (AD) in a patient who has one or more risk factors for AD, comprising administering to a patient in need thereof a therapeutically effective amount of one or more inhibitors of the enzyme 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase, wherein: (a) the HMG CoA reductase inhibitor is not simvastatin, (b) treatment results in a reduction or inhibition of onset of Alzheimer's disease, (c) the one or more risk factors are selected from the group consisting of being 60

years of age or older, being exposed to environmental factors predisposing a patient to AD; having the .alpha.-2-macroglobulin genotype, having the presenilin I mutation for familial AD, having the presenilin II mutation for familial AD, having the amyloid precursor protein (APP) missense mutation for familial AD, having a family history of AD, having prior infection by the herpes simplex virus, and having prior infection by chlamydia pneumoniae, and (d) the patient to be treated does not possess the APOE 4 gene.

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L4: Entry 11 of 11 File: USPT Mar 28, 2000

DOCUMENT-IDENTIFIER: US 6043224 A
TITLE: Compositions and methods for treatment of neurological disorders and neurodegenerative diseases

Brief Summary Text (31):
The invention also contemplates a method by which the overexpression of APP is deliberately effected, followed by the promotion or stimulation of APP metabolism to provide soluble APP (APPs). The former step can be attained by, for example, cAMP signaling, while the latter process can be accomplished, for example, by the activation of protein kinase C (PKC) or of neurotransmitter agonists (e.g., via m1, m3, serotoninergic, or metabotropic glutamate receptors) which increase phophotidylinositol (PI) hydrolysis. Consequently, increased amounts of APPs are secreted into the medium, and the formation of amyloidogenic A.beta. peptides is disrupted. It is believed that secreted APPs have neurotrophic and neuroprotective functions. Secreted APPs have been shown to promote neurite outgrowth and maintain synapse. It is believed further that increased APPs secretion promotes synaptic transmission and neuronal regeneration (e.g., via neurite or axonal outgrowth). The net result is the conversion of an amyloidogenic event (i.e., APP overexpression and A.beta. formation) into a neurotrophic event (i.e., APPs secretion).

Detailed Description Text (36):
As in the methods described above, GFAP expression can be regulated by administering to the subject an effective amount of an anti-inflammatory agent, which are preferably selected from a corticosteroid, glucocorticoid, or an admixture comprising estrogen and estradiol.

CLAIMS:

16. The method of claim 13 in which stimulation of APP metabolism leads to the secretion of soluble APP (APPs) or to other nonamyloidogenic compounds.

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